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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and mplete Specification filed on 18/09/2003 in respect of Patent Application No.977/MUM/2003 of **(a) M/S. RCA LABORATORIES LIMITED, (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, harashtra, India (c) Indian company incorporated under the Companies Act 1956.**

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents ct, 197

CERTIFIED COPY OF PRIORITY DOCUMENT

Dated this 17 th day of Aug 2006.

M.A. Haafeez
(M.A. HAAFEEZ)
ASSTT.CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
[See section 7]

1. We,

   (a) M/S. IPCA LABORATORIES LIMITED

   (b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

   (c) Indian company incorporated under the Companies Act 1956

2. Hereby declare –

   (a) that we are in possession of an invention titled **"A NOVEL PROCESS FOR PREPARATION OF STABILIZED PHARMACEUTICAL ORAL SOLID DOSAGE COMPOSITIONS"**

   (b) that the Complete Specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventor(s) for the said invention are

   (a) Thembalath, Ramachandran

   (b) 6/35, Prakash Co. Housing Society,
   Relief Road, Santacruz (West),
   Mumbai 400 054,
   Maharashtra, India
   (c) Indian National

   (a) Bansal, Yatish Kumar
   (b) Flat No. 3, Siras Villa,
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   Evershine Nagar, Malad (West)
   Mumbai 400 064
   Maharashtra, India
   (c) Indian National

ORIGINAL

977
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Original.

977/MUM/2003

18/9/2003

Received Rs. 3000/- (Rupees Three Thousand only)
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Vide Entry No. 4811 in the Register of Patents, Bombay.

977 MUM 2003
18 SEP 2003

(a) **Singh, Veena**
(b) 4/129, BHEL Officers Flats,
Link Road, D. N. Nagar,
Andheri (West)
Mumbai 400 053
Maharashtra, India
(c) Indian National

(a) **Kotian, Reshma**
(b) B/201, Shivchhaya,
Opposite C. K. P. Colony,
Eksar Road, Borivali (West)
Mumbai 400 091
Maharashtra, India
(c) Indian National

4. That we are the assignee(s) of the true and first inventors.

5. That our address for service in India is as follows:

GOPAKUMAR NAIR ASSOCIATES, NAIR BAUG, AKURLI ROAD, KANDIVLI (EAST), MUMBAI – 400 101.

6. Following declaration was given by the inventor(s) :

We the true and first inventors for this invention in the convention country declare that the applicant(s) herein are our assignee

(Thembalath, Ramachandran)

(Bansal, Yatish Kumar)

(Singh, Veena)

(Kotian, Reshma)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Following are the attachment with the application:
   (a) Complete specification (2 copies)
   (b) Statement and Undertaking on Form 3
   (c) Copy of Form 26 (Original Power of attorney in our favour has been submitted with Application No. 150/MUM/2003)
   (d) Fee Rs.3000/- in cheque bearing No. 583882 dated 18th September, 2003 on Global Trust Bank Limited, Mumbai.

We request that a patent may be granted to us for the said invention.

Dated this the 18th day of September 2003

Dr. Gopakumar G. Nair
Agent for the Applicant
Gopakumar Nair Associates
Nair Baug, Akurli Road, Kandivli (East),
Mumbai – 400 101, Maharashtra, India

To
The Controller of Patents
The Patent Office,
At Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

COMPLETE SPECIFICATION
[See section 10]

"A Novel Process for Preparation of Stabilized Pharmaceutical Oral Solid Dosage Compositions"

(a) **IPCA LABORATORIES LTD.**

(b) 48, Kandivli Industrial Estate, Mumbai – 400 067, Maharashtra, India

(c) Indian Company incorporated under the Companies Act 1956

The following specification describes the nature of the invention and the manner in which it is to be performed:

DUPLICATE

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18 SEP 2003

A NOVEL PROCESS FOR PREPARATION OF STABILIZED PHARMACEUTICAL ORAL SOLID DOSAGE COMPOSITIONS

Technical Field

This invention relates to a novel process of preparing a stabilized oral dosage form of an active pharmaceutical ingredient (API) such as paroxetine hydrochloride and a novel process for improving the stability of the said active pharmaceutical ingredient (API) prior to incorporating into an oral delivery system. This invention further relates to a process for preparation of free flowing granules of paroxetine hydrochloride obtained by coating them with moisture barrier pharmaceutical excipients. More specifically, this invention relates to the process for the preparation of coated granules of paroxetine hydrochloride anhydrate and oral pharmaceutical compositions containing the same.

Background and Prior Art

Paroxetine is chemically described as (-)-trans-4-((4'-flurophenyl)3-3(3'4'-Methylenedioxy phenoxy methyl) - piperidine. Paroxetine has been approved for treating depression in humans.

Paroxetine (API) has first been claimed for its antidepressant properties in US Pat 3,912,743 and US 40007196 (Ferrosan, Denmark). In 1980 paroxetine was licensed to Smithkline, where paroxetine was described as the maleate salt.

Crystalline paroxetine hydrochloride hemihydrate, process for its preparation, compositions containing the same and its preparation, and its therapeutic use as antidepressant has been claimed in US Pat.4721723 and EP 223403.

Thereafter, a large number of patent applications have been filed and patents granted for different forms of the API different pharmaceutical formulations using paroxetine and processes for formulating the same.

Patent WO9958113 describes paroxetine hydrochloride used in amorphous form or in the form of a crystalline anhydrate which is formulated into tablets under conditions such that there is no detectable conversion to hemihydrate during the tabletting process. Such conditions have been achieved by the use of essentially anhydrous or low moisture excipients such as dibasic calcium phosphate anhydrous (A_TAB*), anhydrous direct compression lactose, monosachharide sugars eg mannitol, disaccharide sugars eg lactitol (Finlac DC*), powdered cellulose, pregelatinised starch, microcrystalline cellulose (Avicel PH112*), sodium starch glycolate, croscarmellose sodium(Ac-Di-SolF*), colloidal silicon dioxide (Syloid 244*) (Explotab*), magnesium stearate and talc. Paroxetine hydrochloride anhydrate is mixed with the anhydrous or low moisture excipients and compressed using standard pharmaceutical procedures. As an additional aid to the protection of this product from the deleterious affects of moisture, the tablets are film- coated using hydrophobic coating materials such as glyceryl behenate (Compitrol 888*) using a hot melt coating technique.

Patent WO9958116 uses the same API and excipients for a capsule formulation i.e. paroxetine hydrochloride anhydrate is mixed with anhydrous or low moisture excipients and filled into cellulose capsule shell of intrinsically low moisture content (eg Shiono Qualicaps). The invention also finds that dibasic calcium phosphate anhydrous and polyglycolized glycerides can be used to form oral swallow capsules with paroxetine anhydrate without undesired conversion to hemihydrate during manufacturing process.

Patent WO02102382 describes a process for preparing paroxetine hydrochloride from paroxetine base which provides paroxetine hydrochloride substantially free of pink-colored compounds or an impurity identified by an HPLC RRT of about 1.5.

US Patent. No. 5,955,475 describes an invention where paroxetine free base is formulated into pharmaceutical compositions when adsorbed on or absorbed by a solid carrier.

Patent WO 9831365 elaborates a process for preparing a free flowing form of paroxetine hydrochloride which comprises spray drying a solution of paroxetine hydrochloride. However no discussion appears in the patent regarding the problem of colour development.

US Patent No. 6168805 discloses an invention that relates to a process for preparing solid, amorphous paroxetine comprising a) mixing paroxetine free base or its salt with water and a pharmaceutically acceptable polymer and b) drying to form a composition comprising amorphous paroxetine and polymer, eliminating the need for organic solvents common for the solvent process. The resultant amorphous solid paroxetine composition is free from crystalline form and yet has good handling properties, making it suitable for pharmaceutical use in the traditional tablet dosage form.

Patent WO0102393 complexes of paroxetine, as free base or salt, with cyclodextrin or a cyclodextrin derivative show a high chemical stability, an improved solubility in water and are suitable for the preparation of liquid or solid pharmaceutical compositions.

Patent WO9948499 paroxetine free base is advantageously formulated into pharmaceutical compositions when adsorbed or absorbed by a solid carrier. The composition of this invention is simply obtained by combining a solution of paroxetine with a suitable adsorbent or absorbent material and evaporating the solvent, for example by spray drying.

US patent No. 6503927 describes a stable amorphous paroxetine hydrochloride composition employing an aqueous solvent medium containing an acidulant and polyvinylpyrrolidone and drying the resulting solid dispersion. The preferred compositions include amorphous paroxetine hydrochloride, polyvinylpyrrolidone and citric acid.

WO9926625 provides pharmaceutical formulations of paroxetine in which paroxetine is in solution in a solid, semi-solid or liquid carrier. The solutions are used to fill capsules,

or self-supporting solid solutions are shaped into solid dosage forms such as tablets or pellets.

Patent WO 95/16448 reveals that earlier commercial paroxetine hydrochloride hemihydrate tablets were made using a wet granulation process. Further, the commercial tablets exhibited a colour change i.e. the tablets developed a pink hue that is undesirable.

Patent US2002065301 elaborates paroxetine salt compositions made with the aide of water by controlling the pH to 6.5 or less. These compositions have improved stability without significant coloration problems. The paroxetine salts include paroxetine hydrochloride salts but preferably use paroxetine sulfonate salts such as paroxetine methane sulfonate.

US Patent 6113944 relates paroxetine which is formulated into tablets using a formulation process in which water is absent. Direct Compression technique has been used where paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients and compressed into tablets or by dry granulation techniques as in US Patent No. 6007842 where paroxetine hydrochloride hemihydrate is conventionally admixed with dry excipients and compressed into large slugs or roller compacted into ribbon- like strands. The compacted material is then suitably milled to produce a free flowing powder which is then compressed into tablets. The excipients revealed in the patent include dicalcium phosphate dihydrate (Emcompress* or Ditab*), microcrystalline cellulose (Avicel PH 102*), sodium starch glycollate (Explotab*) & magnesium stearate.

Summary of the Invention

In the present invention, we have provided a novel process for preparation of the active pharmaceutical ingredient with protective coating prior to incorporating into the dosage form. We have thereby conclusively eliminated any possibility of degradation or color development by accelerated stability studies and have introduced characteristics of stability into the solid oral dosage form.

The usage of ethylcellulose provided a hydrophobic coating to the active pharmaceutical ingredient and improved the stability of the product by inhibiting oxidation. Ethylcellulose additionally worked as a binder in the formulation. Granules coated with ethylcellulose demonstrated the added advantage of the ability to absorb compression pressure and hence protect the coating from breaking during compression.

Coated granules of paroxetine hydrochloride anhydrate are disclosed which are prepared using a solution of moisture barrier excipient and a nonionic surfactant in an organic solvent. Such granules are manufactured by preparing a semisolid mass of the API and the solution of moisture barrier coating, preparing strands of suitable diameter of the wet mass, drying the strands and finally milling to get granules of desired size. The granules of the API are then incorporated into solid oral dose formulations of paroxetine. Alternately the coating of powder is obtained by coating fluidized API in a suitable equipment.

Detailed Description

In keeping with our objective of providing long term stability to the oral solid dosage form of paroxetine hydrochloride, we have selected excipients which would contribute to this characteristic objective. We have chosen not to use excipients such as disaccharides such as maltose, lactose, sucrose and glucose. Solvents like water have also not been used.

We have also considered a coating agent which would provide excellent protection against moisture and at the same time immediately release the drug in the gastro-intestinal environment, as desired.

Paroxetine hydrochloride anhydrate has been chosen for experimental trials since it is considered more difficult to protect from moisture. It would also be possible to protect paroxetine hydrochloride hemihydrate using the process cited.

Other attempts were also made with moderate results to use other moisture barrier excipients such as polyethylene glycols, polyglycolised glycerides, fatty alcohols, stearic acid, opadry AMB OY-B-28920 white and opadry 20A 58900 white, fatty materials of plant and animal origin. Additionally the tablets were also film coated with hydrophobic coating materials to retard degradation.

The following examples illustrate the various aspects of the present invention.

EXAMPLE 1

A coating solution of ethylcellulose was made to dissolve in methylene chloride and iso-propyl alcohol. Polysorbate 80 was added to this solution. The active pharmaceutical ingredient was coated with this coating solution. The coated granules formed were dried at a suitable temperature and screened through a mesh of appropriate size. Dicalcium phosphate, microcrystalline cellulose and sodium starch glycollate were milled to which milled citric acid was geometrically mixed. Finally the dried mass of coated active granules were sized appropriately and blended with the above mixture and lubricated with the help of magnesium stearate. These resultant granules could be adequately compressed to tablets or could be suitably filled into hard gelatin capsule shells.

The pharmaceutical composition of the tablets containing paroxetine hydrochloride anhydrate has the following composition.

Paroxetine hydrochloride anhydrate	33.32 mg
Polysorbate 80	2.00 mg
Ethylcellulose (10 cps)	0.33 mg
Methylene chloride; Isopropyl alcohol	1: 3 ratio
Dicalcium phosphate (dihydrate granular)	320.35 mg
Microcrystalline cellulose (Avicel PH 102)	100.00 mg
Sodium starch glycollate (Primogel)	20.00 mg
Citric acid	4.00 mg
Magnesium sterate	5.00 mg

EXAMPLE 2

The moisture retardant coated active pharmaceutical ingredient was prepared by Fluid Bed Processor (GLATT).

Ethyl cellulose was dissolved in the solvent mixture of methylene chloride and isopropyl alcohol. Complete dissolution was ensured and then polysorbate 80 was added to the solution and mixed avoiding foam.

The bowl of the Fluid bed processor (FBP) was loaded with paroxetine hydrochloride anhydrate. The API was fluidized in the FBP and coating solution sprayed through the spray nozzle till coating point was reached which was confirmed at the entrance port on the exterior of the expansion chamber.

- Inlet temp. 60 ° C- 80 ° C
- Product temp. 30°c - 45° C
- Flap opening 25% - 50%
- Spray rate 10% - 20 %
- Atomising air pressure NLT 2.5 Kg/cm2

(iv) The granules were dried to a desired moisture content of NMT 1%

(v) Dicalcium phosphate (dihydrate granular) was added, microcrystalline cellulose (Avicel pH 102), sodium starch glycollate (Primogel), milled citric acid anhydrous and fluidised. Magnesium sterate was added and further fluidized.

(vi) The blend was compressed into tablets using suitable punches.

(vii) The tablets are aqueous film coated using HPMC

EXAMPLE 3

Alternately, the active pharmaceutical ingredient was coated by a moisture barrier solution and granulated by using Rapid Mixer Granulator (RMG).

(i) Coating solution preparation

Ethyl cellulose was dissolved in the solvent mixture of methylene chloride and isopropyl alcohol. Complete dissolution was ensured and polysorbate 80 was added in the solution and mixed avoiding foam.

(ii) The bowl of the Rapid Mixer Granulator (RMG) was loaded with paroxetine hydrochloride anhydrate. The mixer was started at low speed. The coating solution was poured on the bed of the paroxetine hydrochloride powder and mixed till a wet mass was obtained. The wet mass was sized using suitable screens.

(iii) The granules were dried in a fluid bed drier with the following parameters till the moisture content of NMT 1%

- Inlet temp. 60° C- 70° C
- Product temp. 30°C - 45° C

(iv) Dicalcium phosphate (dihydrate garnular), microcrystalline cellulose (Avicel pH 102), sodium starch glycollate (Primogel) and citric acid anhydrous were added and mixed in a double cone blender. Magnesium sterate was added and mixed thereafter.

(v) The resultant blend was compressed into tablets using suitable punches.

(vi) The tablets were aqueous film coated using HPMC

Although this invention has been described with reference to specific embodiments thereof, it is to be understood that other embodiments and variations of the inventions as described and exemplified may be made by those skilled in the art without departing from

the true spirit of invention. It is intended that the appended claims be construed to include all such embodiments and variations.

We claim,

1. A stable oral solid dosage composition of coated granules of active pharmaceutical ingredient prepared in a process characterized in that
   the said process comprises:
   i) granulating a pharmaceutically active ingredient to form a granulated active core;
   ii) preparing moisture barrier coating solution by dissolving ethyl cellulose in a mixture of methylene chloride and isopropyl alcohol;
   iii) adding a non-ionic surfactant such as polysorbate 80 to the said moisture barrier coating solution;
   iv) coating the said active core containing the active pharmaceutical ingredient with the said moisture barrier coating solution
   v) drying till desired moisture content of NMT 1%, blending with other excipients and lubricating the coated granules, and
   vi) compressing the blended granules into tablets using suitable punches.
2. A process as claimed in claim 1, wherein the said active pharmaceutical ingredient is an anti-depressant paroxetine hydrochloride anhydrate.
3. A process as claimed in claim 1, wherein the said active pharmaceutical ingredient is paroxetine hydrochloride hemihydrate.
4. A process as claimed in claim 1, 2 and 3, wherein the coating of the granules is prepared by conventional granulation technique.
5. A process as claimed in claim 1, 2 and 3, wherein the coating of the granules is prepared by fluidization process.
6. A process as claimed in claim 1, 2 and 3, wherein the composition of methylene chloride and isopropyl alcohol used in the ratio of 1:3.
7. A process as claimed in claim 1, 2 and 3, wherein the said excipient is citric acid anhydrous in the formulation.
8. A process as claimed in claim 1, 2 and 3, wherein the said excipients is dicalcium phosphate as a diluent in the formulation.

9. A process as claimed in claim 1, 2 and 3, wherein the said excipients is microcrystalline cellulose as diluent in the formulation.
10. A process as claimed in claim 1, 2 and 3, wherein sodium starch glycollate is used as pharmaceutically acceptable disintegrant in the formulation.
11. A process as claimed in claim 1, 2 and 3, wherein magnesium stearate is used as a pharmaceutically acceptable lubricant in the formulation during tabletting.
12. A process as claimed in claim 1 and 2, wherein the said tablets are caplet shaped.
13. A process as claimed in claim 1, 2 and 3, wherein the granules compressed into tablets with hardness ranging from 150- 200 Newton.
14. A process as claimed in claim 1, 2 and 3, wherein the tablets are optionally coated using conventional film coating materials.
15. A process as claimed in claim1 wherein active ingredient is protected by a moisture barrier coating eliminates the possibility of degradation of active ingredient or development of pink hue in the pharmaceutical formulation.
16. A process as claimed in claim 1, 2 and 3, wherein the said excipients are cyclodextrins, ion-exchange resins, menthol, flavours and colours in the claimed formulation which acts as taste-masking agent.
17. A process as claimed in claim 1, 2 and 3, wherein the coated granules are suitably filled into hard gelatin capsules.
18. Process for preparation of a stable oral solid dosage composition of coated granules of active pharmaceutical ingredient as substantially described herein with reference to the foregoing examples.

Dated this the 18th day of September 2003

Dr. Gopakumar G. Nair
Agent for the Applicant

Abstract

This invention describes a novel process of preparing a stabilized oral dosage form of an active pharmaceutical ingredient (API) such as paroxetine hydrochloride for improving the stability of the active pharmaceutical ingredient (API) prior to incorporating into an oral delivery system. This invention further relates to a process for preparation of free flowing granules of paroxetine hydrochloride obtained by coating them with moisture barrier pharmaceutical excipients. More specifically, this invention relates to the process for the preparation of coated granules of paroxetine hydrochloride anhydrate and oral pharmaceutical compositions thereof.